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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,053	05/10/2001	Stephan Berens	P 280248 000091 BT	3782
909	7590	03/15/2004	EXAMINER	
PILLSBURY WINTHROP, LLP			FRONDA, CHRISTIAN L	
P.O. BOX 10500				
MCLEAN, VA 22102			ART UNIT	PAPER NUMBER

1652

DATE MAILED: 03/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/852,053	<b>Applicant(s)</b> BERENS ET AL.	
	<b>Examiner</b> Christian L Fronda	<b>Art Unit</b> 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 September 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 20, 21 and 24-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24-26 is/are allowed.
- 6) ☒ Claim(s) 20, 21, 27-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### DETAILED ACTION

1. Claims 20, 21, and 24-39 are under consideration in this Office Action.

#### *Claim Rejections - 35 U.S.C. § 112, 1st Paragraph*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20, 30, and 32-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, a vector comprising said polynucleotide, and a recombinant *Corynebacterium glutamicum* comprising said polynucleotide; does not reasonably provide enablement for any other embodiment.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The *Wands* factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any polynucleotide encoding any polypeptide consisting of any amino acid sequence that is at least 90% identical to SEQ ID NO: 3 or SEQ ID NO: 4, any vector containing the claimed polynucleotide, and any recombinant *Corynebacterium glutamicum* comprising the claimed polynucleotide.

The specification provides guidance and examples for making an isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4. However, the specification does not teach the specific structural/catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered. The state of the art as exemplified by Attwood et al. (Comput. Chem. 2001, Vol. 25(4), pp. 329-39) is such that "...we do not fully understand the rules of protein folding, so we cannot predict protein structure; and we cannot invariably diagnose protein function, given knowledge only of its sequence or structure in isolation" (see Abstract and entire publication). Furthermore, Ponting (Brief.

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Bioinform. March 2001, Vol. 2(1), pp. 19-29) states that "...predicting function by homology is a qualitative, rather than quantitative, process and requires particular care to be taken...due attention should be paid to all available clues to function, including orthologue identification, conservation of particular residue types, and the co-occurrence of domains in proteins" (See Abstract and entire publication).

The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed polynucleotide is enormous and entails selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in a polynucleotide to make a polynucleotide that encodes a polypeptide that contains an amino acid sequence that is at least 90% identical to SEQ ID NO: 3 and SEQ ID NO: 4 and determining by assays whether the polypeptide has activity. The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for protein/enzyme structure and activity/function which must be preserved. Thus, searching for the specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in a polynucleotide to make the claimed polynucleotide is well outside the realm of routine experimentation and predictability in the art of success in determining whether the resulting polypeptide has activity is extremely low since no information is provided by the specification regarding the specific catalytic amino acids and the structural motifs essential for enzyme structure and activity/function which must be preserved.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific catalytic amino acids and the structural motifs essential for activity/function which must be preserved. Without such a guidance, the experimentation left to those skilled in the art is undue. Claims 30, 32-39 which depend from claim 20 are also rejected because they do not correct the defect of claim 20.

#### ***Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 27-29 and 31-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.  
The phrase "SEQ ID NO:1 nucleotides 34 to 1944" and the phrase "SEQ ID NO: 2

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nucleotides 22 to 1230" renders claims 27-29 vague and indefinite because the meaning of the phrase is not known and not defined in the specification. Claims 31-39 which depend from claims 27-29 are also rejected because they do not correct the defect of claims 27-29.

Amending the claims to recite the phrase "nucleotides 34 to 1944 of SEQ ID NO: 1" or "nucleotides 22 to 1230 of SEQ ID NO: 2" may overcome the rejection.

### ***Claim Rejections - 35 U.S.C. § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 21, 30, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Billman-Jacobe et al. [Applied and Environmental Microbiology (1994), 60(5), 1641-5] in view of the combined teaching of Smith (U00011) and Van Mellaert et al. [Recent Research Developments in Microbiology (1999), 3(Pt. 2), 425-440].

Billman-Jacobe et al. teach a method for overexpressing and purifying ovine gamma interferon using a recombinant *Corynebacterium glutamicum* as a host cell for high level expression and purification of said ovine gamma interferon wherein said recombinant *Corynebacterium glutamicum* contains a vector comprising a polynucleotide encoding gamma interferon (see entire publication).

Billman-Jacobe et al. do not teach a recombinant *Corynebacterium glutamicum* comprising an isolated polynucleotide encoding a polypeptide "consisting essentially" of the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4 wherein said polypeptide is overexpressed and a vector containing said polynucleotide.

Smith (Accession U00011) teaches a polynucleotide encoding a secD protein (protein secretion factor) having an amino acid sequence "consisting essentially" of the amino acid sequence of SEQ ID NO: 3 (see enclosed alignment US-09-852-053-3 X U00011). Smith (Accession U00011) teaches a polynucleotide encoding a secD protein (protein secretion factor) having an amino acid sequence "consisting essentially" of the amino acid sequence of SEQ ID NO: (see enclosed alignment US-09-852-053-4 X U00011).

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Van Mellaert et al. teach *Corynebacterium glutamicum* has the advantage of being a good candidate for heterologous protein production because it has no broad-spectrum proteolytic activity (see abstract and entire publication).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the recombinant *Corynebacterium glutamicum* taught by Billman-Jacobe et al., wherein the polynucleotide encoding gamma interferon is replaced with the polynucleotide taught by Smith which encodes a secD protein (protein secretion factor) having an amino acid sequence "consisting essentially" of the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for the purposes of high level expression and purification of the secD protein taught by Smith and that *Corynebacterium glutamicum* has the advantage of being a good candidate for heterologous protein production because it has no broad-spectrum proteolytic activity as taught by Van Mellaert et al.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because of the success of Billman-Jacobe et al. in overexpressing and purifying ovine gamma interferon using a recombinant *Corynebacterium glutamicum* as a host cell for high level expression and purification of said ovine gamma interferon.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly prima facie obvious.

### ***Conclusion***

8. Claims 24-26 are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

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3/10/09  
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PRIMARY EXAMINER